UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,589	12/15/2003	Serengulam V. Govindan	328884	2607

63322 7590 09/17/2008

IMMUNOMEDICS, INC.
300 AMERICAN ROAD
MORRIS PLAINS, NJ 07950

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,589	GOVINDAN, SERENGULAM V.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,14,15,17-30,32-34,36-45 and 48-73* is/are pending in the application.

4a) Of the above claim(s) *5-8,61,62 and 69-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,17-30,32-34,36-45,48-50,63-66 and 68* is/are rejected.

7)☒ Claim(s) *14,67* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 6/20/2008 in response to the previous Non-Final Office Action (4/01/2008) is acknowledged and has been entered.

Claims 1, 5-8, 14-15, 17-30, 32-34, 36-45, 48-73 are pending.

Claims 5-8 and 51-62 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 69-73 are withdrawn from consideration as being drawn to non-elected species.

Claims 1, 14-15, 17-30, 32-34, 36-45, 48-50 and 63-68 are currently under consideration.

Species Election

The species of claim 67 appears to be free of the prior art. As such, claim 68 has been chosen as the next species.

Rejections Withdrawn:

The rejection of Claims 1, 15, 17, 18-30, 32-34, 36-45, 48-50 and 63-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 17-24, 27-30, 33-34, 36-43 and 48-50 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001, of record) in view of Hsel et al. (US 7,122,636, filed 2000).

Chari et al teach (page 2, lines 11-14 and page 5, lines 30-31) an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4, which binds to the CD19 antigen on B cells, can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers. With regards to the linking group, Chari et al. teach (page 6, lines 1-2) that suitable linking groups include, but are not limited to, esterase labile groups. Moreover, the WO publication teaches (page 6, lines 4-14, page 7, lines 1-5, page 9, formula II and/or III and page 21, lines 28-30) that the linking group is part of a chemical moiety having a peptide such as N-methyl-cysteine or N-methyl-alanine, covalently bound at the C-terminus to an anti-mitotic agent, such as a maytansinoid derivative, via an ester linkage, e.g., alpha carboxylic acid, and at the N-terminus to the cell-binding agent via a disulfide bond. As a result, the WO publication teaches (page 22, lines 1-2) the conjugates would have 1 to 10 drug molecules per antibody molecule. Moreover, Chari et al. teach (page 30, lines 9-22) that the immunoconjugates may be administered in a suitable form via i.v.. Thus, while Chari et al. do not characterize an antibody specific for an antigen expressed on small cell lung cancer as an antibody specific for an antigen expressed on a carcinoma cell, the claimed functional limitation would be an inherent property because as evidenced by Dictionary.com (see attached), small cell lung cancer is also referred to as small-cell lung carcinoma. Moreover, although Chari et al. does not specifically recite that the immunoconjugate is formulated for parental administration, the claimed functional limitation would be an inherent property because as evidenced by Stedman's Medical Dictionary (see attached), the term parental refers to the introduction of substances to an organism by intravenous, subcutaneous, intramuscular, or intramedullary injection. Thus, the claimed immunoconjugate appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and

functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Chari et al. do not explicitly teach that the linker further comprises a water-solubilizing moiety between the therapeutic moiety and the cell binding agent, wherein the water-solubilizing agent is an aminopolycarboxylate such as PEG.

Hsel et al. teach a conjugated formed by one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules (column 7, lines 29-21). In particular, the patent teaches that the antibodies include, but are not limited to, antibodies comprising an antigen binding site that binds to a polypeptide selected from the group consisting of vascular endothelial growth factor (VEGF), human p185 receptor-like tyrosine kinase (HER2), human CD20, human CD18, human CD11a, human IgE, human apoptosis receptor (Apo-2), human tumor necrosis factor-a (TNF-a), human tissue factor, human a4b7 integrin, human GPIIb-IIIa integrin, human epidermal growth factor receptor (EGFR), human CD3, and human iterleukin-2 receptor a-chain (TAC) (column 7, lines 45-59). Moreover, the patent teaches that the antibodies include bispecific and heteroconjugate antibody fragments having specificities for at least two different antigens (column 64, lines 27-46). With regards to the nonproteinaceous polymer molecules, the patent teaches that nonproteinaceous polymer molecules include, but are not limited to, PEG (column 65, lines 24-60). The patent further teaches that the antibody conjugates can be produced by reacting the free sulfhydryl group of the antibody with a maleimido substituted PEG (column 66, lines 22-48). In addition, the patent teaches that the conjugates can be modified to incorporate one or more small molecule toxins. For example, the patent teaches that maytansine can be converted to May-ss-Me, which is reduced to MaySH3 and reacted with the modified fragment to generate a maytansinoid-derivatized antibody (column 69, lines 39-49). Lastly, the patent teaches that the conjugates exhibit substantially improved half-life, mean residence time, and/or clearance rate in circulation as compared to the underivatized parental antibody fragment (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to modify the conjugate as taught by Chari et al. include a PEG molecule in view of the teachings of Hsel et al.. One would

have been motivated to do so because Hsel et al. clearly teaches conjugating maytansines to PEG-antibody conjugates. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the conjugate as taught by Chari et al. include a PEG molecule in view of the teachings of Hsel et al., one would achieve improved half-life, mean residence time, and/or clearance rate in circulation.

In response to this rejection, Applicants assert that claim 1 recites that the ester bond is between the chemotherapeutic moiety and an alpha amino acid, wherein the alpha amino acid would be understood by one of skill in the art to refer to the 20 naturally occurring amino acids. Hence, Applicants submit that this is significant because intracellular esterases have evolved to cleave ester bonds formed from naturally occurring amino acids. In contrast, Applicants contend that Chari teaches that the ester bond is between the antimitotic drug and carboxylic acid derivatives that are not naturally occurring amino acids. For example, Applicants assert that the N-methylated versions of Chari (see, g. 6-7) are not cleavable by intracellular esterases. Thus, Applicants assert that despite the phrase that"suitable linking groups [include] esterase labile groups" on page 6, Chari uses only the "preferred disulfide groups and thioether groups" and discloses only esters of the N-methylated versions of amino acids. Moreover, Applicants contend that, as stated by the Action "the WO publication teaches... that the linking group is part of the chemical moiety having a peptide such as N-methyl-cysteine or N-methyl-alanine, covalently bound at the C-terminus to an anti-mitotic agent, such as a maytansinoid derivative, via an ester linkage." Hence, Applicants assert that the relevance of this is that intracellular esterases will not recognize an unnatural or an N-alkylated amino acid as a substrate to act on. Thus, Chari fails to teach or disclose the element of attaching a chemotherapeutic moiety to a linker via a intracellularly-cleavable moiety that comprises an ester formed from the alpha-carboxylic acid of an amino acid. In fact, Applicants contend that Chari teaches away from the claimed subject matter by leading the skilled artisan to use linkages not cleavable.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, Applicants arguments appear to center around the notion that alpha amino acids refers to the 20 naturally occurring amino acids; and therefore, would not be recognized by an intracellular esterase. Thus, while the Examiner has carefully considered Applicants reasoning, the Examiner recognizes that Applicants appear to be incorporating limitations which are not recited

in the present claims. For example, the Examiner recognizes that claim 1 recites "an ester formed from the alpha carboxylic acid of an amino acid" Thus, the claims do not infer that that the amino acid is an alpha amino acid, e.g., only a naturally occurring amino acid, as asserted by Applicants, but instead refers to the position of the carboxylic acid from the central carbon, e.g., the alpha carbon, of an amino acid. Secondly, the Examiner recognizes that Applicants arguments appear to be speculative with respect to the definition of an alpha amino acid and only naturally occurring amino acids being susceptible to intracellular esterase without providing any concrete evidence that an alpha amino acid refers to only naturally occurring amino acids. In contrast to Applicants assertions, the Examiner recognizes that all amino acids, naturally occurring or non-naturally occurring, contain an alpha carbon to which is attached a hydrogen, an amino group, a carboxylic group and an R group. For example, all amino acids, naturally occurring and non naturally occurring, contain an alpha carbon which is noted as being the carbon that is directly next to the carboxylic acid, e.g., the 2 carbon in from the C-Terminal. If the amino acid contains a 3rd carbon from the carboxylic acid it would be referred to the beta carbon or in the beta position. The alpha carbon constitutes the backbone of an amino acid. As such, the carboxylic acid next to the alpha carbon can reasonably interpreted as being the alpha carboxylic acid (see for example, the depiction in claim 32). Thus, Chari et al. teachings that the linking group is part of the chemical moiety having a peptide such as N-methyl-cysteine or N-methyl-alanine, covalently bound at the C-terminus to an anti-mitotic agent, such as a maytansinoid derivative, via an ester linkage." (see for example Figure 4 b of Chari) meets the limitation of an ester formed from the alpha carboxylic acid of an amino acid. However, the Examiner recognizes that Applicants appear to be incorporating limitations which are not present in the claims. For example, the instant claims recite "… an ester formed from the alpha carboxylic acid of an amino acid…", which refers to the placement of the carboxylic acid from the the placement of the carboxylic tgroup

Claims 25 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001) in view of Hsel et al. (US 7,122,636, filed 2000), as applied to claims 1, 17-24, 27-30, 33-34, 36-43 and 48-50, in further view of Newton et al. (Blood 2001; 97: 528-535, of record).

Chari et al. in view of Hsel et al. teach an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the conjugate

comprises a water soluble PEG linking group and the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4 which is a murine IgG1, that binds to the CD19 antigen on B cells can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers.

Chari et al in view of Hsel et al. do not explicitly teach that the targeting moiety is the antibody LL2.

Newton et al. teach (abstract) an immunoconjugate comprising LL2 covalently linked to the ribonuclease, onconase, wherein LL2 is an anti-CD22 monoclonal antibody against B-cell lymphoma.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the immunoconjugate as taught by Chari et al. in view of Hsel et al. with a monoclonal LL2 antibody in view of the teachings of Newton et al.. One would have been motivated to do so because as taught by Newton et al., the murine anti-CD22 monoclonal antibody (LL2) was developed for imaging and treatment of non-Hodgkin B-cell lymphomas (NHL). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating LL2 into the immunoconjugate of Chari in view of the teachings of Newton, one would achieve an immunoconjugate which comprises a targeting agent specific for Non-Hodgkin B-cell lymphomas.

In response to this rejection, Applicants assert that Hsel fails to remedy the deficiency of Chari et al., in that it also contains no disclosure relevant to the incorporation of an intracellularly cleavable ester moiety formed from the alpha carboxylic acid of an amino aid.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above.

New Rejections based on Species election:

Claims 63-66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001, of record) in view of Hsel et al. (US 7,122,636, filed 2000, of record), as applied to claims 1, 13-14, 17-24, 27-31, 33-34, 36-43 and 48-50, in further view of Hansen et al. (US 7,312,318, 3/3/2002).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Chari et al. in view of Hsel et al. teach an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the conjugate comprises a water soluble PEG linking group and the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4 which is a murine IgG1, that binds to the CD19 antigen on B cells can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers.

Chari et al in view of Hsel et al. do not explicitly teach that the targeting moiety is the LL2.

Hansen et al. teach a monospecific monoclonal antibody and fragments thereof that recognize a tumor associated antigen defined as CD74 (column 3, lines 12-15) In particular, the patent refers to this antibody as humanized LL1 mAb which comprises CDR regions for the light and heavy chain which encompass the sequences claimed in claim 68 of the instant application (Figure 4). Moreover, the patent teaches that the antibodies are useful for targeting tumor cells, wherein the antibodies are conjugated to a therapeutic agent, including but not limited to, chemotherapeutic agents selected from the group consisting of nitrogen mustard, ethylenimine derivative, alkyl sulfonate, nitrosourea, triazene, folic acid analog, anthracycline, taxane, COX-2 inhibitor, tyrosine kinase inhibitor, pyrimidine analog, purine analog, antibiotic, enzyme, epipodophyllotoxin, platinum coordination complex, vinca alkaloid, substituted urea, methyl hydrazine derivative, adrenocortical suppressant, antagonist, endostatin taxol, camptothecins, doxorubicin, doxorubicin analog, and a combination thereof (column 21, lines 12+).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the immunoconjugate as taught by Chari et al. in view of Hsel et al. with a monoclonal antibody in view of the teachings of Hansen et al. One would have been motivated to do so because as taught by Hansen et al., LL1 antibodies were developed for treatment of tumors, and further, useful as cancer cell targeting therapeutic conjugates. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating RS7 into the immunoconjugate of Chari in view of the teachings of Hansen et al., one would achieve an immunoconjugate which comprises a targeting agent specific for tumors expressing the tumor antigen defined as epithelial glycoprotein-1.

Claims 14 and 67 appear to be free of the prior art, but are objected to for being dependent from a rejected independent claim.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642